PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HSM-LUP-CP2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00003	International filing date *(day/month/year)* 06.01.2003	Priority date *(day/month/year)* 06.01.2003
International Patent Classification (IPC) or both national classification and IPC C07D501/04		
Applicant LUPIN LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.08.2004	15.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kirsch, C Telephone No. +49 89 2399-2191

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00003

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-18 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents :

D1: WO00/66594
D2: WO98/04564
D3: Teh C. Lo, Malcom H.I. Baird, Carl Hanson, 'Handbook of Solvent Extraction', John Wiley & Sons , 1983, pp. 583-591

The present application deals with a process of purification of cefpodoxime proxetil with a ratio of (R/R+S) between 0.5 - 0.6 which consists in an acid-base solvent extraction of impure cefpodoxime proxetil with a ratio of (R/R+S) between 0.5 - 0.6 involving the intermediate formation of the water-soluble methanesulfonic salt of cefpodoxime proxetil.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D1 reveals a process of preparation of cefpodoxime proxetil with a diastereomeric ratio of between 0.5 and 0.6. According to D1, this ratio is achieved by formation of the intermediate N-formyl derivative. After deformylation with an acid, the reaction mixture is quenched with water and potassium hyrogenocarbonate and the precipitate is filtered to give cefpodoxime proxetil with the claimed diastereomeric ratio. Document D1 does not refer to the separation of the cefpodoxime proxetil by solvent extraction and differs therefore from the present invention. Novelty is acknowledged with regard to D1 (Art. 33(2) PCT).

   Document D2 discloses a process for the concentration of 7-ACA and cephalosporin D. This process consists in an acid-base solvent extraction using cyclohexanone as organic solvent. Document D2 does not deal with the purification of cefpodoxime proxetil. The subject-matter of present claims 1-17 is therefore novel over the disclosure of D2 (Art. 33(2) PCT).

   Document D3 is a citation from a book dealing with solvent extraction, which book is considered to be representative of the general knowledge of the skilled man. D3 focuses on the solvent extraction of penicillin and derivatives thereof. According to D3 (p. 584,

2.2. (2)), penicillin can be purified by formation of its salt with an acid. Document D3 does not refer specifically to cefpodoxime proxetil and differs therefore from the present claimed invention (Art. 33(2) PCT).

The subject-matter of claims 1-17 is considered novel with regard to documents D1 to D3 of the prior art (Art. 33(2) PCT).

2. Document D1, which is considered to represent the most relevant state of the art, disclose a process of obtention of purified cefpodoxime proxetil (claim 6) with a ratio of (R/R+S) between 0.5 - 0.6. According to D1, cefpodoxime proxetil is precipitated from the reaction mixture (see example 5) and no solvent extraction, as presently claimed, is described in D1.

The problem to be solved by the present application may therefore be considered as the provision of a process for the purification of cefpodoxime proxetil with a ratio of (R/R+S) between 0.5 - 0.6.

The solution proposed in the present application consists merely in the application of a well-known method for the purification of organic compounds in general and more specifically for the purification of cephalosporin derivatives or analogs thereof. Document D3, which is representative of the general knowledge of the skilled man, stipulates that penicillin (which differs from cephalosporin only on the size of the S-containing ring) may be purified by formation of a salt with an acid (see p. 584, 2.2. (2)-figure 1). According to D3, it is obvious that the impurities are less soluble in water than the intermediate salt formed and that, therefore, the salt can be isolated by separation of the aqueous phase. The penicillin is then regenerated and can be extracted in the organic phase. Such processes are well-known in the art and have been applied to compounds structurally closed from the claimed invention (see also D2).

In his letter of 04.12.2004, the applicant argued that cefpodoxime proxetil contains various functional groups which may not resist an acid-base extraction and that, therefore, the skilled man would not have considered this method of purification to solve the problem posed.

It is to be noted that, according to the process of preparation of cefpodoxime proxetil

(see examples 1-3 according to the application), the compound is isolated after quenching the reaction with hydrochloric acid and washing the organic phase with sodium bicarbonate (base used in the purification process according to the examples of the invention), which merely consists in an acid-base extraction. Since the compound is obtained with a ratio of (R/R+S) between 0.5 - 0.6, there seems to be no reason for the skilled person to think that the compound is unstable under acidic conditions or in the presence of sodium bicarbonate, that the amino group may react in such conditions or that the double bond may isomerize. Furthermore, the process of purification does not involve the use of basic conditions but rather discloses the addition of a base to neutralize the acid, i.e. the pH of the reaction mixture does not exceed 7 (see examples 4-6).

The applicant also emphasized that the fact that the methanesulfonic salt of cefpodoxime proxetil is highly soluble in water compared to other acid addition salts which do not have complete solubility in water. Therefore, the specific use of the methanesulfonic salt would lead to cefpodoxime proxetil free of impurities. Though this assertion could serve to acknowledge the involvement of an inventive step, no comparative data which could demonstrate this effect have been made available so far. In the absence of valid comparative tests, the subject-matter of the present invention may not be considered inventive.

The purification as claimed in the present process is therefore considered to come within the scope of the customary practice followed by persons skilled in the art. Consequently, the subject-matter of claim 1 lacks an inventive step (Art. 33(3) PCT).

Dependent claims 2-17 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.